

## Diuretics are as effective as ACE inhibitors and channel blockers

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Thiazide-type diuretics reduce cardiovascular events as much as angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers in patients with hypertension. This is the finding of the first major study, published just before Christmas, to directly compare different classes of antihypertensives.

The "antihypertensive and lipid lowering to prevent heart attack trial" (ALLHAT), which studied 33 357 people aged 55 years and older with hypertension and at least one other risk factor for coronary heart disease, has been described as one of the most important trials of antihypertensive treatment. The trial was conducted by the ALLHAT Collaborative Research Group in 623 North American centres, and

the findings were published in *JAMA* (2002;288:2981-97).

It randomised the study participants to one of three antihypertensive regimens: the thiazide diuretic chlorthalidone (12.5-25 mg a day; n=15 255); the ACE inhibitor lisinopril (10-40 mg a day; n=9054), and the calcium channel blocker amlodipine (2.5-10 mg a day; n=9048). The goal blood pressure for all patients was <140/90 mm Hg, achieved by titrating the assigned study drug and adding other agents when necessary.

The primary outcome—combined fatal coronary heart disease or non-fatal myocardial infarction—showed no difference between the three antihypertensives. This outcome occurred in 11.5% of people treated with

chlorthalidone over six years, 11.4% in those given lisinopril (relative risk (compared with chlorthalidone) 0.99; 95% confidence interval 0.91 to 1.08), and 11.3% in the amlodipine group (0.98; 0.90 to 1.07). All cause mortality was also similar.

Further results showed that chlorthalidone was more effective—by about 25%—than amlodipine in preventing heart failure. Patients treated with lisinopril showed higher six year rates of combined cardiovascular disease, stroke, and heart failure than those given chlorthalidone.

All three drugs reduced blood pressure substantially, but systolic blood pressures at five years were significantly higher in the groups taking amlodipine (0.8 mm Hg, P=0.03) and lisino-

pril (2 mm Hg, P<0.001) than in the group taking chlorthalidone; the five year diastolic blood pressure was significantly lower in the group taking amlodipine (0.8 mm Hg, P<0.001).

Tolerability was generally similar for the three drugs, with similar rates of hospitalisation for gastrointestinal bleeding. Angio-oedema was four times more common in patients randomised to lisinopril than in those treated with chlorthalidone.

The study was funded by the US National Heart, Lung, and Blood Institute, in Bethesda, Maryland, and Pfizer, and the drugs were supplied by Pfizer (amlodipine and doxazosin), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin). □

### What the findings mean

The researchers concluded: "The results of ALLHAT indicate that thiazide-type diuretics should be considered first for pharmacologic therapy in patients with hypertension. They are unsurpassed in lowering blood pressure, reducing clinical events and tolerability, and they are less costly."

Many participants needed more than one drug to control their blood pressure, so the research team argued that it was reasonable to infer that a diuretic should be included in all multidrug regimens.

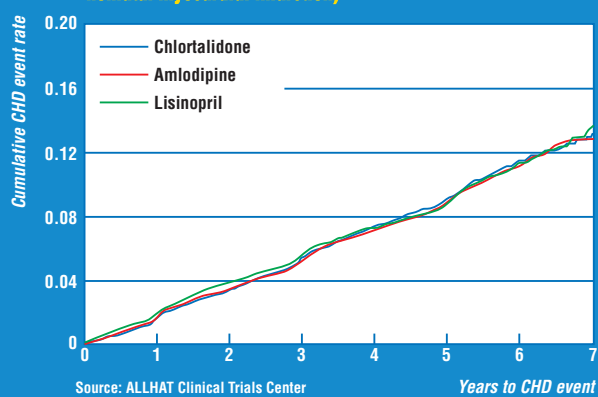
Barry Davis, director of the ALLHAT clinical trial centre and professor of biometry at the University of Texas School of Public Health, Houston, Texas, said: "Previous studies had suggested benefit with some of the newer antihypertensives, but there were no direct comparisons. We found all three agents showed the same effect on [coronary heart disease] and all cause mortality. The thiazide was better at preventing heart failure than the other drugs and better than ACE inhibitors in preventing stroke."

He noted that the National Heart, Lung, and Blood Institute is convening a committee to take account of the ALLHAT findings in the national high blood pressure education programme.

In an editorial published in the same issue of *JAMA*, Lawrence Appel, associate professor of medicine at Johns Hopkins University, Baltimore, commented: "Quite simply, ALLHAT is one of the most important trials of antihypertensive therapy." The class of antihypertensive drugs to use as initial treatment for hypertension has been debated for decades.

Professor Appel wrote: "Resolution of this issue, which has enormous clinical, public health, and economic implications, comes at a time of intense pressure to reduce healthcare costs while improving clinical outcomes." The study showed there was no cost-quality trade-off—the most effective treatment was also the least expensive.

Cumulative event rates for the primary outcome (fatal coronary heart disease (CHD) or nonfatal myocardial infarction)



### Cholesterol drug does not reduce mortality

A subsidiary study showed that lowering cholesterol with pravastatin did not reduce all cause mortality or coronary heart disease compared with usual care (*JAMA* 2002;288:2998-3007).

A subset of 10 355 patients in ALLHAT with low density lipoprotein cholesterol levels of 120-189 mg/dl (3.1-4.9 mmol/l)—or 100-129mg/dl in patients known to have coronary heart disease—were randomised to pravastatin or usual care.

Six year mortality was similar for the two groups—14.9% for pravastatin v 15.3% for usual care (P=0.88).